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Review

Management of infections in critically ill returning travellers in the intensive care unit—II: clinical syndromes and special considerations in immunocompromised patients☆

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SUMMARY

This position paper is the second ESCMID Consensus Document on this subject and aims to provide intensivists, infectious disease specialists, and emergency physicians with a standardized approach to the management of serious travel-related infections in the intensive care unit (ICU) or the emergency department. This document is a cooperative effort between members of two European Society of Clinical Microbiology and Infectious Diseases (ESCMID) study groups and was coordinated by Hakan Leblebicioglu and Jordi Rello for ESGITM (ESCMID Study Group for Infections in Travellers and Migrants) and ESGCIP (ESCMID Study Group for Infections in Critically Ill Patients), respectively. A relevant expert on the subject of each section prepared the first draft which was then edited and approved by additional members from both ESCMID study groups. This article summarizes considerations regarding clinical syndromes requiring ICU admission in travellers, covering immunocompromised patients.
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1. Introduction

Over the last 20 years, the increase in international travel, which has been intensified by the availability of low-cost flights, has facilitated the movement of an increased number of patients from areas with endemic diseases to distant regions. As a consequence, cities around flight hubs have been and are exposed to the rapid dissemination of imported infections, as was reported in the initial dissemination of HIV infection in North America, and more recently in the 2009 influenza pandemic. Similarly, outbreaks of cholera have been reported in travellers after long distance flights, and tourism has also been associated with the dissemination of infections such as measles, rubella, diphtheria, typhoid fever, and chicken pox, in addition to malaria and haemorrhagic fevers. Poor health conditions and crowding are associated with tuberculosis (TB), diarrhoea, tetanus, and other infectious events, which may be imported by migrants from areas devastated by war.

Immunocompromised patients encompass a growing population with increased susceptibility to infectious complications. Because they live longer and have a better quality of life than ever before, they may have more opportunity to travel and potentially encounter travel-associated infections. It has been estimated that up to one third of solid-organ transplant (SOT) recipients may travel to resource-limited countries within the first year post-transplant.[1] In a survey in North American transplant centres, up to 44% of haematopoietic stem cell transplant (HSCT) recipients reported travel outside the USA and Canada after transplantation.[2] A

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significant number of immunocompromised patients may also be migrants who may return to their countries of origin to visit friends and relatives, and may acquire travel-associated infections. The increased use of monoclonal antibodies for therapy in immunological and oncological diseases has created another at-risk population, although the actual risk of travel-associated infection in these patients is not well established.[3] Data on the real risk of infection in immunocompromised travellers relative to the general travel population are scarce,[4] and particularly the risk of developing an illness severe enough to warrant admission to an intensive care unit (ICU). The repatriation of immunocompromised patients from hospitals in destination countries also carries the risk of contamination of the receiving hospital with multidrug-resistant (MDR) microorganisms, which requires specific infection control measures.[5] This article also addresses certain specific syndromes, such as pneumonia and acute respiratory distress syndrome (ARDS) occurring after travel.

This position paper is the second ESCMID Consensus Document on this subject and aims to provide intensivists, infectious disease specialists, and emergency physicians with a standardized approach to the management of serious travel-related infections in the ICU or emergency department. This document is a cooperative effort between members of two European Society of Clinical Microbiology and Infectious Diseases (ESCMID) study groups and was coordinated by Hakan Leblebicioglu and Jordi Rello for ESGITM (ESCMID Study Group for Infections in Travellers and Migrants) and ESGCIP (ESCMID Study Group for Infections in Critically Ill Patients), respectively. A relevant expert on the subject of each section prepared the first draft, which was then edited and approved by additional members from both ESCMID study groups. This article summarizes considerations regarding clinical syndromes requiring ICU admission in travellers, covering immunocompromised patients.

2. Risk of infection in immunocompromised patients (Table 1)

2.1. Solid-organ and haematopoietic stem cell transplantation

The risk of infection in SOT recipients varies according to multiple factors, namely the type of organ transplanted, the time from transplantation, and the type and dose of immunosuppressive drugs received.[6] During the first month post-transplant, infectious complications are mainly healthcare-associated. The most profound immunosuppression occurs between months 2 to 6; historically, this is the period in which most opportunistic infections were diagnosed, including herpesvirus infections (cytomegalovirus), *Pneumocystis jirovecii* pneumonia, and invasive fungal infections.[7] However, with the use of universal antiviral preventive strategies and long-term co-trimoxazole prophylaxis, opportunistic infections are currently rarely seen. After 6–12 months, the risk of infection decreases significantly and infections over this period are usually community-acquired, except in the case of increased immunosuppression (due to allograft rejection or dysfunction) or in the case of chronic surgical complications. Because the incidence of infection is higher early after transplantation, it is recommended to avoid travel during the first year.[8]

HSCT recipients are at increased risk for bacterial and fungal infections during the engraftment period in the first month post-transplant. In the case of graft-versus-host disease, cellular immunosuppression is the mechanism responsible for the development of viral infections (particularly cytomegalovirus, adenovirus, and BK virus) and invasive fungal infections.[9] After the second year post-transplant it is considered that the degree of immunosuppression is non-significant if the patient has not developed chronic complications.

Table 1
Infectious risk according to type of immunosuppression

	Infectious risk	Type of immunosuppression	Type of infection
SOT recipients	1st month post-transplantation: risk related with surgery and ICU stay	Neutrophils: 0 B-cells: + T-cells: ++	Ventilator-associated pneumonia (Pseudomonas, enterobacteria), catheter-related infection, surgical site infection, invasive candidiasis
	1st year post-transplantation: period of higher immunosuppression	Neutrophils: 0/+ B-cells: + T-cells: +++	Viral infections (cytomegalovirus, BK virus, HCV reactivation), fungal infections (Aspergillus, Pneumocystis)
	After 1st year post-transplantation: long-term immunosuppressive therapy	Neutrophils: 0/+ B-cells: + T-cells: +	Community-acquired infections (pneumonia, urinary tract infection), community-acquired respiratory viruses (influenza, RSV), zoster, opportunistic infections in the case of chronic allograft dysfunction
HSCT recipients	1st month post-transplantation: risk related with neutropenia	Neutrophils: +++ B-cells: + T-cells: +	Bacterial infections (Gram-positive bacteria, enterobacteria, Pseudomonas), fungal infections (Candida, Aspergillus)
	1st year post-transplantation: period of higher immunosuppression; immunosuppressive therapy for GVHD	Neutrophils: ++ B-cells: ++ T-cells: +++	Viral infections (cytomegalovirus, adenovirus, HSV, BK virus), fungal infections (Aspergillus, Pneumocystis)
	After 1st year post-transplantation: non-significant immunosuppression >2 years		
Oncological patients	After recent chemotherapy or radiotherapy (particularly in the case of neutropenia and anaemia)	Neutrophils: +++ B-cells: 0/+ T-cells: 0/+	Bacterial infections (Gram-positive bacteria, enterobacteria, Pseudomonas), viral infections (HSV)
Splenectomized patients	Particularly during the first 2 years, but may persist several years after splenectomy	Neutrophils: 0 B-cells: + T-cells: 0	*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*, *Capnocytophaga canimorsus*
Patients receiving anti-TNF therapy	During therapy and a month after discontinuation of anti-TNF drugs	Inhibition of macrophage activation, recruitment of neutrophils, and granuloma formation	Tuberculosis, skin and soft tissue infection, zoster

GVHD, graft versus host disease; HCV, hepatitis C virus; HSCT, haematopoietic stem cell transplant; HSV, herpes simplex virus; ICU, intensive care unit; RSV, respiratory syncytial virus; SOT, solid-organ transplant; TNF, tumour necrosis factor.

2.2. Patients receiving biological agents and others immunotherapies

While the use of biological agents for the therapy of rheumatological and autoimmune diseases has increased considerably over recent years, data on the risk of infection are mainly limited to the use of anti-tumour necrosis factor (TNF) agents. Several large cohort studies found patients receiving anti-TNF therapy to be at greatest risk of developing skin infections, although the overall risk of severe infections was similar to that of patients receiving other non-biological therapies.[10] A study from the Netherlands assessed the risk of infection in 75 travellers receiving biological agents relative to their travelling companions.[4] Immunocompromised patients were at significantly higher risk of developing skin infections, fatigue, and abdominal pain, but not fever, diarrhoea, or respiratory infections. Of note, no serious infection developed during or after the trip in these patients. Patients on anti-TNF therapy have an increased risk of developing mycobacterial infections, with several cases of disseminated TB with a fatal outcome reported in the literature.[11] Cutaneous leishmaniasis has also been reported in patients on anti-TNF treatment.[12]

2.3. Oncological patients

The risk of bacterial and fungal infections in patients with an oncological condition is increased during the administration of chemotherapy and/or radiotherapy and/or immunotherapy, particularly during the period of neutropenia.[13] In contrast, the risk of infection is generally considered not to be increased some months after the conclusion of chemotherapy and in patients receiving hormone therapy. Patients with haematological conditions, such as lymphoma or Hodgkin disease, may, however, have some degree of cellular immunosuppression even months after the remission of the disease.

2.4. Asplenic patients

Asplenic patients are at significantly higher risk of infection with encapsulated bacteria, namely *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*, and *Capnocytophaga canimorsus*.[14] Thus, appropriate vaccination with conjugated vaccines is an essential preventive strategy in these patients. Other potentially life-threatening infections that are more common in asplenic patients include salmonellosis, babesiosis, and malaria. While the risk of infection is higher during the first month following splenectomy, the increased risk persists for years. The risk of infection in asplenic patients depends on the underlying condition, being higher in patients with haematological diseases and in those in whom immunization may not be fully successful or is associated with suboptimal protection over long periods of time. Such patients may be instructed to start empirical antibiotics targeted at encapsulated bacteria immediately if any clinical signs or symptoms of infection ensue.[15]

3. Travel-related infections in immunocompromised patients

3.1. Malaria

There are few studies that have addressed the epidemiology and clinical manifestations of malaria in immunocompromised patients. The incidence of malaria was reported to be less than 1% in HSCT recipients in an endemic country (Pakistan); however, data on other immunosuppressive conditions and in travellers are missing.[15] Despite the lack of prospective studies, it appears that malaria is associated with more severe outcomes in immunocompromised patients than in the general population. A recent systematic review found that up to 45% of published cases of malaria in SOT recipients had at least one criterion for severe malaria (O. Manuel, personal communication). Importantly, malaria may develop through transmission from the organ donor, and as such there may not be a travel history.[16] A case of cerebral malaria with >50% parasitemia has been reported in a patient receiving infliximab;[17] however such severe disease can occur in patients not on biologicals as well. Malaria can also be more severe in splenectomized patients due to the lack of clearance of intra-erythrocytic parasites.

The successful treatment of severe malaria in immunocompromised patients has been reported with the use of erythropheresis and artesunate.[18] The choice of the preventive strategy for malaria in immunocompromised travellers should be individualized, favouring antimalarial prophylaxis in patients travelling to intermediate-risk and high-risk regions.

3.2. Dengue

Several cases of severe dengue in immunocompromised patients have been reported, mostly in patients in endemic countries. In a series of kidney transplant recipients in India, up to 37% of patients diagnosed with dengue had a severe course and died.[19] All presented with fever, thrombocytopenia, myalgia, and retro-ocular pain. In contrast, in a series of eight patients receiving biologicals who were diagnosed with dengue, none developed severe infection.[20] Dengue fever was reported to be a frequent cause of febrile neutropenia in haematological patients in India, but this was not associated with worse outcomes.[21] Early diagnosis is essential in immunocompromised travellers with clinical manifestations suggestive of dengue in order to initiate early appropriate supportive therapy. Aggressive volume replacement within the first 24 h of ICU admission is important to limit the development of multiple organ dysfunction syndrome and increase the probability of survival.

3.3. Fungal infections

Travel-related fungal infections in immunocompromised patients are uncommon, but potentially associated with a severe course and increased mortality.[22] Invasive travel-related fungal infections that have manifested with a severe course in SOT recipients and HIV-infected individuals include disseminated *Penicillium marneffei* infection, aspergillosis, histoplasmosis, and coccidioidomycosis.[23] In patients receiving monoclonal antibodies, severe travel-associated histoplasmosis has been associated with a 50% mortality rate, and in another report, malignancy was a risk factor for acquiring a *Cryptococcus gattii* infection.[24] Importantly some of these infections may have a long incubation period so the travel history may be underreported. As such, a detailed travel history should be sought in immunocompromised travellers who develop fever associated with pulmonary lesions and/or localized cutaneous or subcutaneous disease, and these patients should be investigated promptly and aggressively for the diagnosis of invasive fungal infections.[22]

3.4. Other infections

The risk of TB is increased in transplant patients, HIV-infected individuals, and in patients receiving biologicals, but the risk of travel-acquired TB in immunocompromised patients is not well established. Screening for latent TB infection after travel to endemic regions in these patients might, however, identify patients at risk of developing active TB. Leptospirosis is a common cause of fever in returning travellers, and can be associated with severe complications. In a series of nine HIV-infected patients with

leptospirosis, 67% presented with severe sepsis and the mortality was 22%.[25] Data on the severity of leptospirosis in other immunocompromised populations are lacking. Nocardiosis in SOT recipients is associated with a high incidence of disseminated disease, particularly with central nervous system involvement. Strongyloidiasis in immunocompromised patients is a rare but potentially life-threatening condition. Donor-derived or travel-acquired infestation with *Strongyloides stercoralis* is associated with a high mortality.[26] Cases of Chagas disease (*Trypanosoma cruzi*) either as a consequence of reactivation of a latent infection not identified at the time of transplant (because an unrecorded travel history or stay in an endemic area) or by transmission through the organ donor, can also be associated with a high mortality.[27] Furthermore, immunocompromised patients may be particularly susceptible to severe forms of West Nile virus infection and tick-borne encephalitis, all of which should be actively sought in the workup of patients with central nervous system symptoms after returning from endemic areas. There have also been case reports of severe disease from other travel-associated infections, such as salmonellosis, *Vibrio parahaemolyticus*, and visceral leishmaniasis in immunocompromised patients.

4. Acute respiratory distress syndrome (ARDS) in returning travellers

There are many causes of respiratory failure and of ARDS. Those that are specific to certain geographic regions and that may appear unexpectedly in travellers are less common, but are nevertheless extremely important because appropriate therapy requires a correct diagnosis, and some infections may have epidemic potential. The infectious causes in particular may not be recognized immediately because they may be out of their usual geographical context. Those that can cause ARDS will be discussed briefly below. Table 2 summarizes the main recommended antimicrobial regimens for specific organisms involved in ARDS in returning travellers.

4.1. Community-acquired pneumonia (CAP)

CAP is the most likely cause of acute respiratory failure in returning travellers. The usual pathogens, such as *S. pneumoniae*, *H. influenzae*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Legionella pneumophila*, and viruses such as influenza and respiratory syncytial virus, are the most common culprits. However aspiration must be considered in the elderly and in those who have become inebriated whilst on holiday. Less common pathogens such as *Staphylococcus aureus*, avian influenza viruses such as H7N9 and H5N1, the Middle East respiratory syndrome coronavirus (MERS-CoV), and Gram-negative rods such as *Burkholderia pseudomallei* must also be considered, as well as a few other pathogens that do not usually cause pneumonia, such as malaria.

4.2. Influenza

Influenza viruses such as H1N1 and H3N2, which are currently circulating, are perhaps the most common travel-related infections, particularly in the unvaccinated, those travelling across hemispheres, and where the available vaccine does not cover a particular strain effectively. Influenza is an acute illness manifested by pyrexia, cough, chills, myalgia, and fatigue. There can, however, be more severe complications, specifically pneumonia, especially in pandemic years. In the 2009 influenza A(H1N1)pdm09 pandemic, more than 18 500 deaths were reported, with global estimates 15 times higher. The primary risk factors were age (young to middle age; >60% were aged <65 years), morbid obesity, pregnancy, and an immunocompromised status. Influenza also increases the risk of bacterial pneumonia, particularly that caused by *S. pneumoniae* and *S. aureus*. Those with severe disease deteriorate acutely after 4–5 days, with profound hypoxemia, shock, and often multiple organ dysfunction syndrome. The pathological findings are of an intense inflammatory/haemorrhagic pneumonia, the severity of which seems to be influenced by the presence or absence of associated bacterial CAP.[28]

Any patient with the above features, particularly if unvaccinated or having travelled to another hemisphere during the winter season, should be investigated for influenza, with diagnosis based on throat swab or nasal wash and a commercial kit based on antigen or RT-PCR.[29] Unfortunately there is very low uptake of influenza vaccine even amongst healthcare workers, and as such there remains a large pool of susceptible individuals.

Although not yet reported to have been transmitted from humans, avian influenza H5N1 and H7N9 remain a potential threat, particularly in Southeast Asia. Travellers who have had contact with birds in the affected areas and who present with

Table 2
Recommended antimicrobial therapy for specific organisms involved in acute respiratory distress syndrome (ARDS) in returning travellers

	Recommended regimen	Alternative regimen	Comments
Streptococcus pneumoniae	Penicillin	Second- or third-generation cephalosporin	Penicillin usually effective for non-susceptible strains
Staphylococcus aureus	Methicillin-susceptible: oxacillin, cloxacillin, flucloxacillin Methicillin-resistant: vancomycin or linezolid	Methicillin-susceptible: first-generation cephalosporin or amoxicillin–clavulanic acid Methicillin-resistant: ceftaroline, trimethoprim–sulfamethoxazole	Add clindamycin or linezolid in case of suspicion of PVL-producer Do not use daptomycin for *S. aureus* pneumonia
Legionella pneumophila	Quinolone or macrolide		Despite the absence of RCTs, quinolones are usually recommended over macrolides for severe infections
Pseudomonas aeruginosa	Piperacillin–tazobactam, fourth-generation cephalosporins or carbapenems ± aminoglycoside or quinolones	Colistin in case of infection by MDR strains	Ceftolozane–tazobactam could be an option for therapy of MDR organisms Consider combined inhaled colistin and/or aminoglycoside for MDR
Melioidosis	Ceftazidime or meropenem ± trimethoprim–sulfamethoxazole	Trimethoprim–sulfamethoxazole or doxycycline	
Tuberculosis	(See text)		
Influenza	Oseltamivir, inhaled zanamivir	IV peramivir or IV zanamivir in case of severe infection	Start as soon as possible, empirically in severe cases
RSV	None	Oral or inhaled ribavirin	

IV, intravenous; PVL, Panton–Valentine leukocidin; MDR, multidrug-resistant; RCT, randomized controlled trial; RSV, respiratory syncytial virus.

otherwise unexplained ARDS should be screened. H5N1 has been reported from 17 countries and is currently most prevalent in Egypt.[30]

4.3. Staphylococcus aureus

Staphylococcus aureus pneumonia is usually a fulminant disease associated with rapid onset respiratory failure, frequently progressing to multiple organ dysfunction, shock, and death. Complications are frequent and include pulmonary necrosis and abscess and empyema formation, particularly if the strain is a producer of Panton–Valentine leukocidin (PVL) toxin, a cytotoxin responsible for leukocyte destruction and tissue necrosis. Risk factors are colonization or infection with *S. aureus* and a preceding influenza-like illness (ILI). Leucopenia (2.5×10^9/l) is characteristic and may be an inverse biomarker of PVL burden.[31]

Both methicillin-sensitive *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) can cause CAP. The latter is primarily a problem of recognition, as the organism is not prevalent in all countries and standard guideline-based therapies for pneumonia do not cover MRSA. The sensitivity profile of community-acquired MRSA differs from that of hospital-acquired MRSA in that it may be susceptible to macrolides, quinolones, clindamycin, and trimethoprim–sulfamethoxazole. Therapy consists of appropriate antimicrobial therapy such as linezolid (possibly in preference to vancomycin, particularly if the strain is a PVL-producer), vancomycin, or ceftaroline.[32]

4.4. Legionnaires' disease (legionellosis)

Pneumonia is the most common presentation of legionnaire's disease or legionellosis, and it may be severe, leading to multiorgan failure and death. Characteristic clinical findings are relative bradycardia, hyponatremia, elevation in serum creatinine kinase, diarrhoea, confusion, and impaired liver and kidney function.[33] The recommended treatment regimen is macrolides or fluoroquinolones.[34]

4.5. Middle East respiratory syndrome coronavirus (MERS-CoV)

Ten years after the severe acute respiratory syndrome (SARS) epidemic that affected almost 8000 people and caused 775 deaths, MERS-CoV, a new coronavirus of the same family, appeared in Saudi Arabia and subsequently spread to nine countries in or near the Arabian Peninsula and 14 countries elsewhere.[35] On March 10, 2015, the World Health Organization global case count was 1060 laboratory-confirmed cases with 394 deaths (37%). All cases were resident in or had travelled to the Middle East, most to Saudi Arabia, or had been in contact with travellers returning from these areas. MERS-CoV differs from SARS-CoV in that it binds to different receptors, and camels are thought to be the primary reservoir host, although the means of transmission from these animals is poorly understood. Whereas transmission can occur between humans, the epidemic potential appears to be less. The disease is not always severe and symptoms range from an ILI to severe pneumonia requiring mechanical ventilation. The most severely affected patients have mostly had comorbidities such as diabetes, renal failure, and chronic lung disease, or have been immunocompromised.[36] There is no specific antiviral treatment available for MERS-CoV infection. Management is primarily supportive, directed towards the prevention of respiratory complications and infection control. Corticosteroids are not currently recommended in this setting.

It is still advised that those travelling to the Middle East and who are at increased risk of severe disease should avoid contact with camels and their secretions, and avoid drinking raw camel milk (which will also prevent infection with Brucella). All travellers should practice good hand and food hygiene, particularly where camels are present.

4.6. Gram-negative pathogens

A number of Gram-negative pathogens may cause pneumonia and ARDS, in particular in relation to aspiration, or in association with ventilation where pathogens such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Escherichia coli*, and other *Enterobacteriaceae* are of concern.[37] The latter include the extended-spectrum beta-lactamase (ESBL)- and carbapenemase-producers (such as those producing New Delhi metallo-β-lactamase 1 (NDM-1)), which may be acquired during 'medical tourism'.[38] Diagnosis requires a high index of suspicion and testing for the specific genes responsible for enzyme production. Treatment remains a challenge due to deficiencies in the antibiotic pipeline.

4.7. Melioidosis

Burkholderia pseudomallei is also a Gram-negative bacillus endemic in Southeast Asia, northern Australia, and possibly the Indian subcontinent, southern China, Hong Kong, and Taiwan. Infection results from inoculation of contaminated soil and surface water through skin abrasions, with subsequent haematogenous spread. Horizontal transmission also occurs, as well as transmission through the inhalation of polluted water. It is the most common cause of fatal community-acquired bacteraemia and pneumonia in certain areas of north-eastern Thailand, as well as in Darwin, Australia.[39] Travellers from endemic areas, especially in the wet season and particularly if there are comorbidities, are at risk. Variable disease severity and the range of presentations (pneumonia, abscesses, osteomyelitis, and arthritis) make diagnosis a challenge. About 50% of patients present with pneumonia (which may appear as nodular infiltrates or air space consolidation), often with septic shock. The diagnosis is made when *B. pseudomallei* is cultured, but specific media are required. Ceftazidime or meropenem with or without high-dose co-trimoxazole are the drugs of choice.

4.8. Tuberculosis

Although TB may occur in any patient, it seldom causes respiratory failure over a short period of time. Yet, a recent prospective study from South Africa reported that 1.5% of adults with active TB may require mechanical ventilation because of refractory hypoxemia, which in high TB prevalence countries translates into a significant burden of disease.[40] In this setting, 15% of TB suspects had confirmed TB, and it should be considered if the travel history involves relevant exposure. Standard smear microscopy or culture are used for diagnosis, or rapid PCR if available (GeneXpert MTB/RIF), which has been shown to have increased sensitivity and shorten the time to treatment.[41] Where there is a high clinical suspicion of TB, empiric therapy should be initiated after adequate sampling has been obtained, particularly in the case of life-threatening or disseminated infection. Initial therapy with four drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) is generally recommended where there is a low prevalence of resistance, and depending on the patient's origin and the results of the rapid detection of *rpoB* gene mutations. Patients with MDR- or XDR-TB need to be treated with second-line agents including aminoglycosides, quinolones, para-aminosalicylic acid, cycloserine, and clofazimine, and new drugs such as bedaquiline, linezolid, and delamanid.

4.9. Malaria

Malaria, which is a frequent travel-related disease, may also lead to ARDS in severely affected patients.[41] Increased alveolar capillary permeability may result in pulmonary oedema and respiratory failure either at presentation or after treatment. Pregnant women are particularly at risk. Slide microscopy and rapid antigen tests are the standard diagnostic tools, and the treatments of choice are the parenteral artemisinins, although resistance is emerging.

4.10. Differential diagnosis

Non-infectious causes of bilateral pulmonary infiltrates with respiratory failure must be differentiated from infectious causes. These include cardiogenic pulmonary oedema, inflammatory pulmonary diseases such as cryptogenic organizing pneumonia (COP) and fibrosis, alveolar haemorrhage (including idiopathic granulomatous polyangiitis, lupus, and vasculitis), and ARDS from conditions such as eosinophilic pneumonia, pancreatitis, inhalational injury, and trauma. To identify these, clinical expertise is critical, along with the use of biomarkers (such a C-reactive protein, procalcitonin, and pro-B-type natriuretic peptide), serology to exclude autoimmune diseases, and imaging including echocardiography.

4.11. Rescue therapies for ARDS

If mechanical ventilation alone is inadequate, the use of neuromuscular blockade, recruitment techniques including prone ventilation, and veno-venous extracorporeal membrane oxygenation (ECMO) may improve oxygenation and the outcome.

4.12. Scoring systems for the stratification of patients with severe infection

The Berlin classification of ARDS severity is universally accepted and should be utilized to determine the site of therapy.[42] The Acute Physiology and Chronic Health Evaluation (APACHE) score provides additional information regarding ICU and hospital outcomes.[43] For pneumonia, the most frequently used scores are the pneumonia severity index (PSI) and CURB-65. To evaluate mortality risk in TB patients, the TBscore is useful and has been shown to predict the outcome.[44]

5. Fever with haemorrhagic manifestations

Haemorrhagic symptoms and fever can be caused by many infections due to bacteria, viruses, and parasites. Disseminated intravascular coagulation (DIC) may be a manifestation of severe septicaemia and can be caused by almost all Gram-positive and Gram-negative bacteria. DIC is particularly present in septicaemia with *N. meningitidis* (Figure 1), but is also seen in patients with *S. aureus* and *S. pneumoniae* bloodstream infections (Figures 2 and 3). Numerous viruses may also cause haemorrhagic symptoms, and these include dengue virus, Crimean-Congo haemorrhagic fever virus, Ebola virus, Yellow fever virus, Hanta virus, and others (Table 3).

5.1. Isolation and patients with haemorrhagic symptoms at admission

It is most important to establish whether the patient has a history of travel within the past 4 weeks to areas where viral haemorrhagic fevers are endemic immediately at admission (Table 3). If the history and the clinical features are suggestive,

Figure 1. Ecchymosis in meningococcal septicaemia.

Figure 2. Gangrene complicating *Staphylococcus aureus* septicaemia.

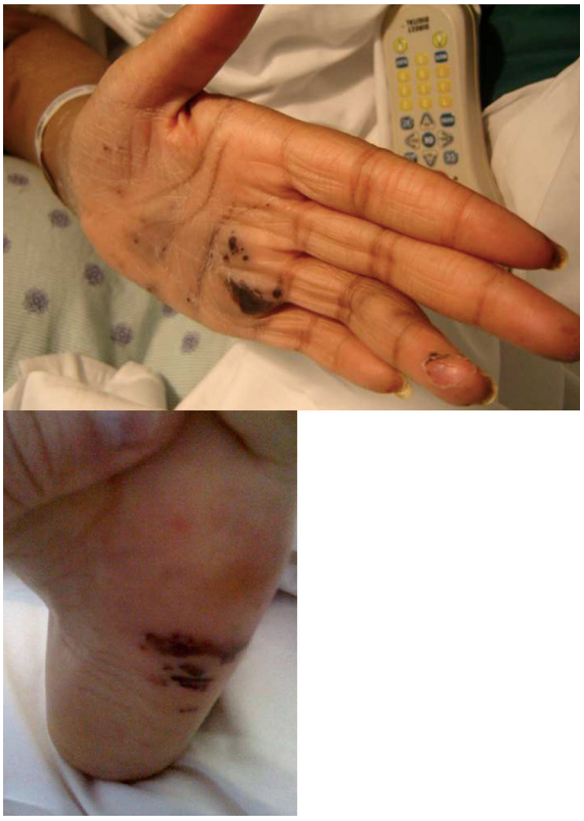

Figure 3. Septic embolisms from left-sided endocarditis.

Table 3
Distribution and endemicity of viral haemorrhagic fevers

	Countries where outbreaks have occurred	Countries with evidence of endemicity, through sporadic cases or seroprevalence studies	Countries/areas with a theoretical risk based on geography, but no reports of cases
Ebola and Marburg	Republic of Congo, Democratic Republic of Congo, Gabon, Ivory Coast, Sudan, Uganda, Liberia, Sierra Leone, Guinea	Central, Western, and East African countries	Tropical Africa South of the Sahara
Marburg	Angola, Democratic Republic of Congo, Kenya, Uganda, South Africa, Zimbabwe	Zimbabwe	Central and East African countries
Lujo	South Africa (ex-Zambia)	-	-
Lassa	Guinea, Liberia, Nigeria, Sierra Leone	Benin, Burkina Faso, Ghana, Ivory Coast, Mali, Togo	Cameroon, Central African Republic, other West African countries
CCHF	Bulgaria, China, Iraq, Iran, Kazakhstan, Kosovo, Mauritania, Oman, Pakistan, Russia, South Africa, Tajikistan, Turkey, United Arab Emirates, Uganda, Uzbekistan	Benin, Burkina Faso, Egypt, France, Greece, Hungary, India, Kenya, Portugal, Tanzania, Zaire	Africa, Balkans, Central Asia, Eastern Europe, Middle East
Hantaviruses	Bosnia, Serbia, Greece (Dobrava), China, Russia, Korea (Hantaan), Scandinavia, Russia, Western Europe (Puumala), Europe (Saaremaa), Worldwide (Seoul)	-	-
South American haemorrhagic fevers	Argentina (Junin), Venezuela (Guanarito), Brazil (Sabia), Bolivia (Machupo, Chapare)	-	-
Kyasanur Forest disease	India	-	-
Alkhurma haemorrhagic fever	Saudi Arabia	-	-
Omsk haemorrhagic fever	Russia	-	-
Dengue haemorrhagic fever	Asia, South America, Tropical Africa	-	Southern Europe

CCHF, Crimean-Congo haemorrhagic fever.

further details should be obtained, as shown in Table 4, and the patient should be evaluated as to whether isolation is necessary.

In most countries where haemorrhagic fever viruses occur, malaria is also endemic, and a malaria test (rapid diagnostic test or microscopy) should be performed immediately and at the same time as blood cultures for bacterial infections are obtained. Once malaria has been excluded, treatment should be started to cover a broad range of bacterial infections until such time as the diagnosis is confirmed. An example of gangrene related to severe staphylococcal septicaemia is shown in Figure 2.

5.2. Rapid assessment

Rapid assessment of the patient and isolation are key to limiting healthcare-associated transmission. The MERS-CoV outbreak in South Korea illustrates how rapidly infections can spread in overcrowded hospitals.[45] Most MERS-CoV cases in Saudi Arabia have also been linked to transmission in hospitals,[46] as was the case with SARS-CoV[47] and with Crimean-Congo haemorrhagic fever.[48] Training of paramedical staff, nurses, and physicians, as well as guidelines for the recognition and rapid assessment of febrile patients at the initial point of contact, are essential, as is an isolation area for febrile patients with a relevant travel history.

5.3. Disseminated intravascular coagulation

DIC is an acquired condition of the vascular system leading to an uncontrolled systemic activation of the coagulation pathway. The generation of thrombin and fibrin may cause thrombotic occlusions of blood vessels, and hence organ injury and failure.[49] This is accompanied by an inflammatory reaction, further augmenting the coagulation process.

DIC frequently accompanies systemic inflammatory response syndrome (SIRS), severe sepsis, trauma, and other conditions as diverse as anaphylaxis and heat stroke.[49–54] The systemic activation of the clotting system is associated with the consumption of both coagulation factors and platelets, and as such, various combinations of platelet count, prothrombin time, activated partial thromboplastin time (aPTT), a decrease in anti-thrombin (AT) and protein C, as well plasma levels of fibrin and D-dimers have been used for the diagnosis.[55] A more standardized approach can be achieved by using the scoring system of the International Society of Thrombosis and Haemostasis.[56]

The successful therapy of DIC is only possible when the underlying cause is identified and treated. The substitution of coagulation factors is currently unclear due to the lack of appropriate randomized placebo-controlled trials. The use of antifibrinolytics during DIC should be avoided, as this drug class may lead to the deposition of fibrin in the vascular walls.[57]

Overall, the prevalence of DIC during viral haemorrhagic fever is high and contributes to morbidity and mortality. Early and effective treatment against the viral infection, if available, reduces the detrimental complications of DIC. Parameters for assessing DIC and haemolysis are provided in Table 5.

Table 4
Questions to be asked if the patient has travelled in an area where haemorrhagic fever occurs

Does the patient have a fever (>38 °C) or history of fever in the previous 24 hours?
AND
Has the patient cared for/come into contact with body fluids of/handled clinical specimens (blood, urine, faeces, tissues, laboratory cultures) from a live or dead individual or animal known or strongly suspected to have VHF?
Has the patient received a tick bite and/or crushed a tick with their bare hands and/or travelled to a rural environment where contact with livestock or ticks is possible in a CCHF endemic area?
Has the patient lived or worked in basic rural conditions where Lassa, Ebola, or Marburg fever is endemic, i.e., West/Central Africa or South America?
Has the patient travelled to any local area where a VHF outbreak has occurred?

CCHF, Crimean-Congo haemorrhagic fever; VHF, viral haemorrhagic fever.

Table 5
Parameters analysed to determine if the patient has disseminated intravascular coagulation (DIC) and haemolysis

Platelet count
Plasma fibrinogen
Plasma anti-thrombin
Plasma fibrin degradation products
Plasma D-dimer
Plasma coagulation factor II, VII, X (INR)
Plasma coagulation factors II, VII, X (PT)
Plasma coagulation, thrombin time
Plasma coagulation, surface-induced (aPTT)
Haemolysis
Bilirubin
Reticulocytes
Lactate dehydrogenase
Free haemoglobin
Haptoglobin
Coombs test
Urine for haemosiderin

aPTT, activated partial thromboplastin time; INR, international normalized ratio; PT, prothrombin time.

5.4. Bacteraemia

Patients with suspected severe sepsis should be managed according to standard guidelines.[58] These include broad-spectrum antibiotics, aggressive initial fluid replacement, blood pressure support if needed, the correction of acidosis, and oxygenation by intubation and mechanical ventilation as needed. Echocardiography is essential to evaluate cardiac function and any vegetations on the cardiac valves. In the initial stages it is difficult to differentiate between a viral haemorrhagic fever, severe bacterial sepsis, and severe malaria.

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JR and HL designed the manuscript: OM and PE wrote the immunocompromised host section, GR and CW wrote the ARDS section, and CW, EP and KZ wrote the haemorrhagic fever section. OM and JR assembled the final version. All authors read and approved the last version of the manuscript.

References

1. Boggild AK, Sano M, Humar A, Salit I, Gilman M, Kain KC. Travel patterns and risk behavior in solid organ transplant recipients. *J Travel Med* 2004;**11**:37–43.
2. Mikati T, Griffin K, Lane D, Matasar M, Shah MK. International travel patterns and travel risks for stem cell transplant recipients. *J Travel Med* 2015;**22**:39–47.
3. Bialy C, Horne K, Dendle C, Kanellis J, Littlejohn G, Ratnam I, et al. International travel in the immunocompromised patient: a cross-sectional survey of travel advice in 254 consecutive patients. *Intern Med J* 2015;**45**:618–23.
4. Baaten GG, Geskus RB, Kint JA, Roukens AH, Sonder GJ, van den Hoek A. Symptoms of infectious diseases in immunocompromised travelers: a prospective study with matched controls. *J Travel Med* 2011;**18**:318–26.
5. Vila J. Multidrug-resistant bacteria without borders: role of international trips in the spread of multidrug-resistant bacteria. *J Travel Med* 2015;**22**:289–91.
6. Fishman JA. Infection in solid-organ transplant recipients. *N Engl J Med* 2007;**357**:2601–14.
7. Manuel O, Kralidis G, Mueller NJ, Hirsch HH, Garzoni C, van Delden C, et al. Impact of antiviral preventive strategies on the incidence and outcomes of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant* 2013;**13**:2402–10.
8. Kotton CN, Hibberd PL, Practice ASTIDCo. Travel medicine and transplant tourism in solid organ transplantation. *Am J Transplant* 2013;**13**(Suppl 4):337–47.
9. Wingard JR, Hsu J, Hiemenz JW. Hematopoietic stem cell transplantation: an overview of infection risks and epidemiology. *Infect Dis Clin North Am* 2010;**24**:257–72.
10. Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP, et al. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum* 2006;**54**:2368–76.
11. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 2001;**345**:1098–104.
12. Catala A, Roe E, Dalmau J, Pomar V, Muñoz C, Yelaomos O, et al. Anti-tumour necrosis factor-induced visceral and cutaneous leishmaniasis: case report and review of the literature. *Dermatology* 2015;**230**:204–7.
13. Kamana M, Escalante C, Mullen CA, Frisbee-Hume S, Rolston KV. Bacterial infections in low-risk, febrile neutropenic patients. *Cancer* 2005;**104**:422–6.
14. Di Sabatino A, Carsetti R, Corazza GR. Post-splenectomy and hyposplenic states. *Lancet* 2011;**378**:86–97.
15. Shamsi T, Hashmi K, Adil S, Ahmad P, Irfan M, Raza S, et al. The stem cell transplant program in Pakistan—the first decade. *Bone marrow transplant* 2008;**42**(Suppl 1):S114–7.
16. Chiche L, Lesage A, Duhamel C, Salame E, Malet M, Samba D, et al. Posttransplant malaria: first case of transmission of *Plasmodium falciparum* from a white multiorgan donor to four recipients. *Transplantation* 2003;**75**:166–8.
17. Geraghty EM, Ristow B, Gordon SM, Aronowitz P. Overwhelming parasitemia with *Plasmodium falciparum* infection in a patient receiving infliximab therapy for rheumatoid arthritis. *Clin Infect Dis* 2007;**44**:e82–4.
18. Sabe N, Gonzalez-Costello J, Oriol I, Sanchez-Salado JC, Ortega S, Oliver E, et al. Donor-transmitted malaria after heart transplant managed successfully with artesunate. *Transplant Infect Dis* 2014;**16**:999–1002.
19. Prasad N, Bhadauria D, Sharma RK, Gupta A, Kaul A, Srivastava A. Dengue virus infection in renal allograft recipients: a case series during 2010 outbreak. *Transplant Infect Dis* 2012;**14**:163–8.
20. Deligny C, de Bandt M, Dehlinger V, Numeric P, Cabie A, Lombard F, et al. Dengue fever in patients under biologics. *J Clin Virol* 2014;**61**:442–3.
21. Jain H, Sengar M, Menon H, Dangi U, Biswas S, Chandrakanth MV. Dengue fever as a cause of febrile neutropenia in adult acute lymphoblastic leukemia: a single center experience. *Hematol Oncol Stem Cell Ther* 2014;**7**:125–6.
22. Lortholary O, Charlier C, Lebeaux D, Lecuit M, Consigny PH. Fungal infections in immunocompromised travelers. *Clin Infect Dis* 2013;**56**:861–9.
23. Singh N, Huprikar S, Burdette SD, Morris MI, Blair JE, Wheat LJ, et al. Donor-derived fungal infections in organ transplant recipients: guidelines of the American Society of Transplantation, infectious diseases community of practice. *Am J Transplant* 2012;**12**:2414–28.
24. MacDougall L, Fyfe M, Romney M, Starr M, Galanis E. Risk factors for *Cryptococcus gattii* infection, British Columbia, Canada. *Emerg Infect Dis* 2011;**17**:193–9.
25. Biggs HM, Galloway RL, Bui DM, Morrissey AB, Maro VP, Crump JA. Leptospirosis and human immunodeficiency virus co-infection among febrile inpatients in northern Tanzania. *Vector Borne Zoonotic Dis* 2013;**13**:572–80.
26. Abanyie FA, Gray EB, Delli Carpini KW, Yanofsky A, McAuliffe I, Rana M, et al. Donor-derived *Strongyloides stercoralis* infection in solid organ transplant recipients in the United States, 2009–2013. *Am J Transplant* 2015;**15**:1369–75.
27. Jackson Y, Dang T, Schnetzler B, Pascual M, Meylan P. *Trypanosoma cruzi* fatal reactivation in a heart transplant recipient in Switzerland. *J Heart Lung Transplant* 2011;**30**:484–5.
28. Napolitano LM, Angus DC, Uyeki TM. Critically ill patients with influenza A(H1N1)pdm09 virus infection in 2014. *JAMA* 2014;**311**:1289–90. http://dx.doi.org/10.1001/jama.2014.2116
29. Centers for Disease Control and Prevention. Rapid diagnostic testing for influenza: information for health care professionals. Atlanta, GA: CDC; 2015. Available at: http://www.cdc.gov/flu/professionals/diagnosis/rapidclin.htm (accessed March 25, 2015).
30. World Health Organization. Avian influenza A(H7N9) virus. Geneva: WHO; 2015. Available at: http://www.who.int/influenza/human_animal_interface/influenza_h7n9/en/ (accessed March 25, 2015).
31. Francis JS, Doherty MC, Lopatin U, Johnston CP, Sinha G, Ross T, et al. Severe community-onset pneumonia in healthy adults caused by MRSA carrying the Panton–Valentine leukocidin genes. *Clin Infect Dis* 2005;**40**:100–7.
32. Vazquez JA, Maggiore CR, Cole P, Smith A, Jandourek A, Friedland HD. Ceftaroline Fosamil for the treatment of *Staphylococcus aureus* bacteremia secondary to acute bacterial skin and skin structure infections or community-acquired bacterial pneumonia. *Infect Dis Clin Pract* 2015;**23**:39–43.
33. Jespersen S, Søgaard OS, Schønheyder HC, Fine MJ, Ostergaard L. Clinical features and predictors of mortality in admitted patients with community- and hospital-acquired legionellosis: a Danish historical cohort study. *BMC Infect Dis* 2010;**10**:124.
34. Yu VL, Ramirez J, Roig J, Sabria M. Legionnaires disease and the updated IDSA guidelines for community-acquired pneumonia. *Clin Infect Dis* 2004;**39**:1734–7.
35. Centers for Disease Control and Prevention. Middle East respiratory syndrome (MERS). Atlanta, GA: CDC; Available at: http://www.cdc.gov/coronavirus/mers/accessed (accessed March 18, 2015).
36. Breban R, Riou J, Fontanet A. Interhuman transmissibility of Middle East respiratory syndrome coronavirus: estimation of pandemic risk. *Lancet* 2013;**382**:694–9.
37. Charles MP, Easow JM, Joseph NM, Ravishankar M, Kumar S, Sivaraman U. Aetiological agents of ventilator-associated pneumonia and its resistance pattern—a threat for treatment. *Australas Med J* 2013;**6**:430–4.
38. Kuster SP, Hasse B, Huebner V, Bansal V, Zbinden R, Ruef C, et al. Risk factors for infections with extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* at a tertiary care university hospital in Switzerland. *Infection* 2010;**38**:33–40.
39. Foong YC, Tan M, Bradbury RS. Melioidosis: a review. *Rural and Remote Health* 2014;**14**:2763.
40. Calligaro G, Theron G, Khalfey H, Peter J, Meldau R, Matinyenya B, et al. A randomised controlled trial of the impact of Xpert-MTB/RIF on tracheal aspirates nested within a burden of disease study in South African intensive care units. *Lancet Respir Med* 2016. in press.
41. Marks M, Gupta-Wright A, Doherty JF, Singer M, Walker D. Managing malaria in the intensive care unit. *Br J Anaesth* 2014;**113**:910–21.

42. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin definition. ARDS Definition Task Force. *JAMA* 2012;**307**:2526–33.
43. Breslow MJ, Badawi O. Severity scoring in the critically ill: part 1—interpretation and accuracy of outcome prediction scoring systems. *Chest* 2012;**141**:245–52.
44. Rudolf F, Lemvik L, Verkuilen J, Abate E, Schön T, Eugen-Olsen J, et al. TBscoreII: refining and validating a simple clinical score for treatment-monitoring patients with pulmonary tuberculosis. *Scand J Infect Dis* 2013;**45**:825–36.
45. Petersen E, Hui DS, Perlman S, Zumla A. Middle East respiratory syndrome—advancing the public health and research agenda on MERS— lessons from the South Korea outbreak. *Int J Infect Dis* 2015;**36**:54–5.
46. Oboho IK, Tomczyk SM, Al-Asmari AM, Banjar AA, Al-Mugti H, Aloraini MS, et al. 2014 MERS-CoV outbreak in Jeddah—a link to health care facilities. *N Engl J Med* 2015;**372**:846–54.
47. Centers for Disease Control and Prevention. Cluster of severe acute respiratory syndrome cases among protected health-care workers—Toronto, Canada, April 2003. *MMWR Morb Mortal Wkly Rep* 2003;**52**:433–6.
48. Pshenichnaya NY, Nenadskaya SA. Probable Crimean-Congo hemorrhagic fever virus transmission occurred after aerosol-generating medical procedures in Russia: nosocomial cluster. *Int J Infect Dis* 2015;**33**:120–2.
49. Levi M, ten Cate H. Disseminated intravascular coagulation. *N Engl J Med* 1999;**341**:586–92.
50. Bakhtiari K, Meijers JC, de Jonge E, Levi M. Prospective validation of the International Society of Thrombosis and Haemostasis scoring system for disseminated intravascular coagulation. *Crit Care Med* 2004;**32**:2416–21.
51. Gando S. Disseminated intravascular coagulation in trauma patients. *Semin Thromb Hemost* 2001;**27**:585–92.
52. Saba HI, Morelli GA, Saba RI. Disseminated intravascular coagulation (DIC) in cancer. *Cancer Treat Res* 2009;**148**:137–56.
53. Weiner CP. The obstetric patient and disseminated intravascular coagulation. *Clin Perinatol* 1986;**13**:705–17.
54. Levi M. Disseminated intravascular coagulation. *Crit Care Med* 2007;**35**:2191–5.
55. Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. *Br J Haematol* 2009;**145**:24–33.
56. Taylor Jr FB, Toh CH, Hoots WK, Wada H, Levi M. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost* 2001;**86**:1327–30.
57. Mannucci PM, Levi M. Prevention and treatment of major blood loss. *N Engl J Med* 2007;**356**:2301–11.
58. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;**41**:580–637. http://dx.doi.org/10.1097/CCM.0b013e31827e83af